

Fig.1. Kynurenine pathway and related enzymes. Abbreviations: IDO, indoleamine 2,3-dioxygenase; TDO, tryptophan 2,3-dioxygenase; PLP, pyridoxal 5' phosphate; HAD, 3-hydroxyanthranilate 3,4-dioxygenase; QPRT, quinolinate phosphoribosyltransferase

FIG. 1

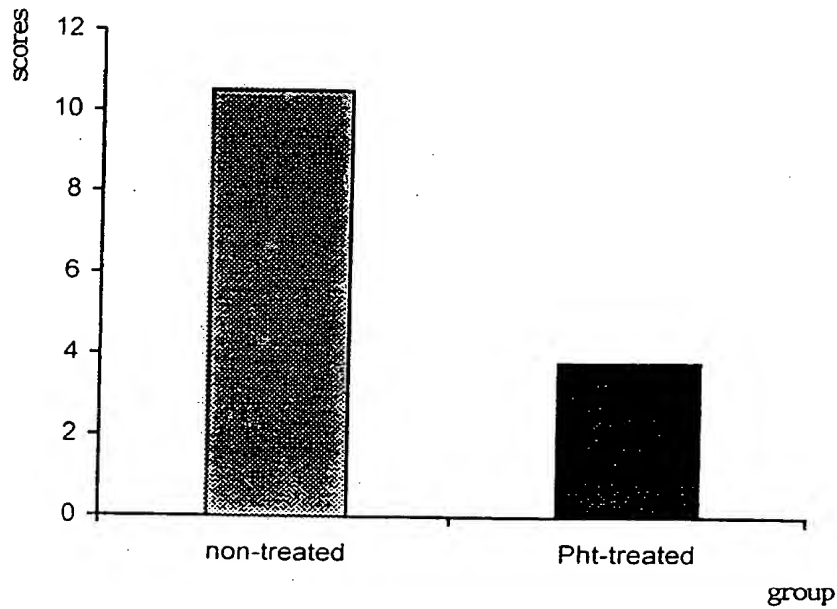
APPROVED	FIG.
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Table 1
 Plasma kynurenines in epilepsy-prone (EP) rats and rats with spontaneous non-convulsive
 absence seizures (GAERs) in comparison with control epilepsy-resistant (ER) rats
 Effect of anticonvulsive drugs (phenytoin and ethosuximide) on plasma kynurenines

	TRP	KYN	3HOKYN	3HOAA	AA	KA	KA/3HOAA	(AA+KA)/3HOAA
ER	43.5±1.4	3.4±1.5		10.7±6.5	188.6±37.1	260.0±227.5	37.9±33.5	55.4±29.2
EP	59.0±7.6	0.5±0.2		18.5±2.3	411.4±122.4	21.1±9.6	1.1±0.5	23.3±6.5
EP/Pht chronic.	38.8±14.0	3.1±0.8		13.4±3.4	446.3±31.2	370.5±253.6	45.8±39.3	74.2±56.6
GAERs	54.8±9.4	0.9±0.4		13.2±4.1	111.6±60.2	42.5±30.0	3.6±2.7	13.0±10.8
GAERs/Ets		6.1±2.7	0.8±0.2	21.6±3.5	930.0±150.5	672.0±208.0	37.9±12.9	85.8±31.9
GAERs/Ets chronic.	28.1±2.2	0.37±0.03		23.6±6.5	142.7±54.6	36.6±22.2	1.4±0.5	8.4±3.1

FIG. 2

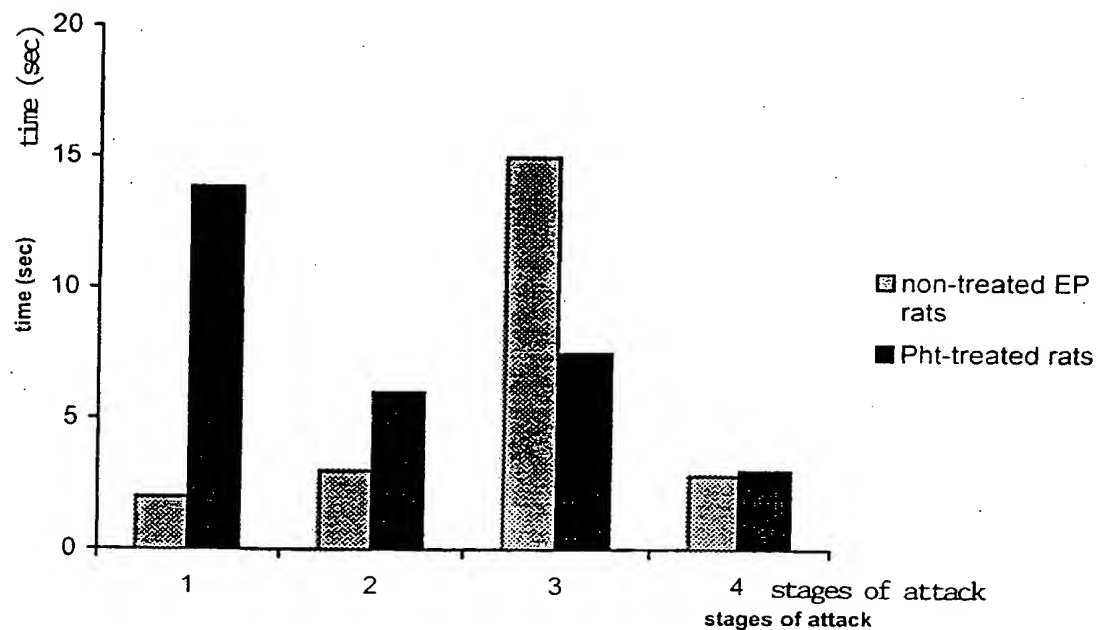
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**Scores:**

- 0 --absence of reactions
- 1 --short-term wild running
- 2 --two phase wild running
- 4 --tonic convulsions of flexors
- 6 --tonic convulsions of extensors
- 8 --postictal excitation or muscular atonia
- 10 -postictal excitation with convulsions
- 12 -postictal coma
- 16 -lethal exit

FIG. 3A

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**Stages of attack:**

1. Latency
2. Wild running
3. Tonic convulsions of flexor or/and extensors
4. Clonic convulsions

Postictal condition	Non-treated	Pht
immobility	0/9	11/11
excitation	3/9	0/11
coma	6/9	0/11

FIG. 3B

APPROVED	O. G. FIG.
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Brain kynurenines in epilepsy-prone (EP) rats in comparison with control epilepsy-resistant (ER) rats (per 1g tissue)

The effect of phenytoin

cortex

Table 2

Metabolites	TRP	KYN	3HOKYN	3HOAA	AA	KA	3HOAA/TRP
	mkM	mkM	mkM	nM	nM	nM	
EP	49.0±3.2	(3/6)	< 0.01	374.7±35.9	202.6±43.6	282.1±124.1	7.7 ± 0.6
EP/Pht	57.6±5.4		< 0.01	417.2±82.6	3(6)	1(6)	7.3±1.8
ER	42.5±7.6	1.63±1.2	< 0.01	271.2±40.3	< 1.0	(1/5)	6.6 ± 1.3

midbrain

Metabolites	TRP	KYN	3HOKYN	3HOAA	AA	KA	3HOAA/TRP
	mkM	mkM	mkM	nM	nM	nM	
EP	100.2±19.8	(2/5)	(1/5)	380.0±49.0	180.7±165.5	115.4	3.8 ± 0.3
EP/Pht	145.3±44.1	(1/3)	< 0.01	464.0±184.8	< 1.0	(2/6)	3.2±0.4
ER	80.4±21.0	(1/6)	(2/6)	368.3±74.6	< 1.0	< 1.0	4.6 ± 0.4

brain stem

Metabolites	TRP	KYN	3HOKYN	3HOAA	AA	KA	3HOAA/TRP
	mkM	mkM	mkM	nM	nM	nM	
EP	84.1±15.8	0.39	0.11	221.6±25.5	69.7±11.6	(3/6)	2.7 ± 0.3
EP/Pht	97.2±19.1	3.48	< 0.01	288.3±120.9	59.1±42.7	484.6	2.7±0.7
ER	104.0±11.4	0.56±0.23	(2/6)	288.0±52.0	< 1.0	(1/6)	2.8 ± 0.4

cerebellum

Metabolites	TRP	KYN	3HOKYN	3HOAA	AA	KA	3HOAA/TRP
	mkM	mkM	mkM	nM	nM	nM	
EP	40.8±8.3	0.38±0.3	0.07±0.055	36.4±18.0	(2/5)	81.1±52.2	0.9 ± 0.4
EP/Pht	47.6±10.3	0.83	< 0.01	159.5±70.6	(2/4)	(1/4)	3.3±0.8
ER	41.6±1.2	0.16	(2/6)	98.9±28.1	< 1.0	< 1.0	2.4 ± 0.6

*/ in brackets the numbers of individual measurements out of the number of analysed samples are indicated

FIG. 4

APPROVED	Q. 5. FIG.
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Table 3

Brain kynurenines in rats with spontaneous non-convulsive absence seizures (GAERs) in comparison with epilepsy-resistant (ER) rats (per 1g tissue).

Effect of ethosuximide

Metabolites	TRP	KYN	3HOKYN	3HOAA	AA	KA	3HOAA/TRP
	mkM	mkM	mkM	nM	nM	nM	
ER	42.5±7.6	1.63±1.2	<0.01	271.2±40.3	<1.0	(1/5)	6.6±1.3
GAERs	66.45±3.4	<0.01	<0.01	464.75±85.2	<1.0	(1/7)	7.0±1.3
GAERs Ets	40.8±6.9	(1/10)	<0.01	250.6±62.8	(4/10)	(1/10)	6.1±1.0
GAERs Ets chronic.	60.5±5.8	(2/6)	<0.01	572.8±62.8	<1.0	<1.0	9.5±1.7

midbrain

Metabolites	TRP	KYN	3HOKYN	3HOAA	AA	KA	3HOAA/TRP
	mkM	mkM	mkM	nM	nM	nM	
ER	80.4±21.0	(1/6)	(2/6)	368.3±74.6	<1.0	<1.0	4.6±0.4
GAERs	78.6±20.9	<0.01	<0.01	272.4±55.8	<1.0	<1.0	3.5±0.5
GAERs ETS	51.0±26.2	(2/10)	<0.01	280±69.1	235.9±45.4	(2/10)	7.3±4.3
GAERs Ets chronic.	92.4±23.7	(2/6)	<0.01	235.3±68.0	<1.0	<1.0	2.7±0.8

brain stem

Metabolites	TRP	KYN	3HOKYN	3HOAA	AA	KA	3HOAA/TRP
	mkM	mkM	mkM	nM	nM	nM	
ER	104.0±11.4	0.56±0.23	(2/6)	288.0±52.0	<1.0	(1/6)	28±0.4
GAERs	116.2±16.5	0.33±0.18	<0.01	315.3±127.8	<1.0	(1/7)	2.6±0.7
GAERs Ets	49.9±7.9	0.18±0.15	<0.01	200.3±42.7	(1/10)	(4/10)	4.1±0.8
GAERs Ets chronic.	76.7±23.7	0.43±0.38	<0.01	196.7±45.5	<1.0	<1.0	2.6±0.3

cerebellum

Metabolites	TRP	KYN	3HOKYN	3HOAA	AA	KA	3HOAA/TRP
	mkM	mkM	mkM	nM	nM	nM	
ER	41.6±1.2	0.16	(2/6)	98.9±28.1	<1.0	<1.0	2.4±0.6
GAERs	40.8±5.73	(1/7)	(3/7)	70.5±18.2	<1.00	(2/7)	1.7±0.4
GAERs Ets	26.4±2.4	(1/10)	<0.01	56.4±54.9	(1/10)	(2/10)	2.1±1.8
GAERs Ets chronic.	41.3±3.5	0.26±0.09	(1/6)	122.7±65.1	<1.0	<1.0	4.2±1.7

* / in brackets the numbers of individual measurement out of the number of analysed samples are indicated

FIG. 5

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APPROVED	Q.9. FIG.
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Plasma kynurenines in seizure-free epileptic patients and patients non-controlled by Antiepileptic drugs, in comparison with healthy children

Table 4

	TRP	KYN	3HOAA	AA	KA	AA+KA	KA/3HOAA	(AA+KA)/3HOAA	KA/3HOAA/TRP	(KA+AA)/3HOAA/TRP
Seizure-free	25.7±3.1	1.0±0.2	7.0±3.3	5.1±1.5	34.8±5.8	39.8±7.9	5.0±1.5	5.7±2.6	0.16±0.04	0.22±0.08
Non-controlled	20.8±3.5	0.8±0.2	3.8±1.1	7.1±3.9	24.2±4.9	27.8±9.1	6.3±2.2	8.1±3.0	0.30±0.07	0.40±0.12
Healthy	29.8±4.9	1.3±0.3	8.6±4.8	4.4±2.8	21.9±8.5	23.4±9.8	2.6±1.6	3.1±2.6	0.09±0.02	0.1±0.06

FIG. 6

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Plasma kynurenines in patients with repeated febrile convulsions in comparison with healthy children and children after the first episode of febrile convulsions

Table 5

	TRP	KYN	3HOAA	AA	KA	AA+KA	KA/3HOAA	(AA+KA)/3HOAA	KA/3HOAA/TRP	(KA+AA)/3HOAA/TRP
Healthy	29.8±4.9	1.3±0.3	8.6±4.8	4.4±2.8	21.9±8.5	23.4±9.8	2.6±1.6	3.1±2.6	0.09±0.02	0.10±0.06
Repeated febrile convulsions	28.0±1.8	1.2±0.5	14.6±6.3	7.1±3.2	22.3±8.9	29.4±10.7	1.5±0.5	2.0±0.4	0.05±0.01	0.07±0.02
Febrile convulsions with family history	33.4±7.9	3.0±1.8	11.3±6.3	4.5±2.0	25.0±9.6	29.6±11.4	3.2±1.6	3.9±3.1	0.12±0.04	0.11±0.07
Febrile convulsions without history	28.4±7.9	2.3±0.8	11.4±8.9	13.2±5.8	29.0±11.2	42.2±17.9	2.8±1.3	5.7±3.1	0.13±0.07	0.20±0.10

FIG. 7